UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,046	11/20/2001	Frederic J. de Sauvage	P1405R1C1	1433

9157 7590 04/28/2010

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
04/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,046	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/9/10 has been entered.

Status of Application, Amendments and/or Claims

On 3/9/10, Applicants filed a response to the previous Office Action that includes a listing of claims which does not include any claim amendments (each pending claim listed as "Previously Presented"). This claim listing has been entered.

Claims 29, 30, 36-40, 46-49 and 52-54 are pending in the application.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 30, 36-40, 46-49 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al (18 February 1998. Nat Genet. 18(2): 104-6; cited previously) in view of Tso et al (U.S. Patent No. 5,932,448, published 8/3/88, and filed 11/29/1991; cited previously). This rejection was set forth previously and maintained at pg 2-4 of the 11/9/09 Office Action.

Applicants' arguments (3/9/10; pg 4-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants first argue that "[a]nticipation is a doctrine that states that the claimed subject matter was known in the prior art, not that the claimed subject matter could have been known in the prior art through the combination of various teachings" (pg 5). Applicants argue that the "Doctrine of Inherent Anticipation was devised to address anticipation by something that existed in the prior art, but may have unrecognized" and the rejection stretches said doctrine "beyond its intended boundaries".

These arguments have been fully considered but are not persuasive for the following reasons. The instant rejection is not based on anticipation under 35 U.S.C. 102, but instead is based on obviousness under 35 U.S.C. 103, and thus explicitly relies on the combination of teachings of Motoyama et al and Tso et al. As stated in MPEP 2112, "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103 "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness"" (citing *In re Napier* (1995)).

Applicants further argue that the rejection combines "a teaching of Patched-2 protein with a general method of making antibodies to state that antibodies against the mouse Patched-2 are obvious" and then states "that such a theoretical pool of antibodies would inevitably and always contain antibodies that also specifically bound human Patched-2 protein (despite the fact that no such protein was ever described prior to the Applicants' disclosure)" (pg 5).

These arguments have been fully considered but are not persuasive for the following reasons. This section of Applicants' response is a restatement of the grounds of rejection and is not disputed. The fact that Tso et al is a "general method of making antibodies" does not detract from the obviousness of combining it with a reference such as Motoyoma et al that teaches the isolation of a new protein. The Board of Patent Appeals and Interferences has taken the position that once an antigen has been isolated, the manufacture of antibodies which include polyclonal and monoclonal antibodies against it, is *prima facie* obvious. See *Ex parte Ehrlich*, 3 USPQ 2d 1011 (PTO Bd. Pat App. & Int. 1987), *Ex parte Sugimoto*, 14 USPQ 2d 1312 (PTO Bd. Pat. App. & Int. 1990). With regard to the "pool of antibodies" being "theoretical", it is noted

that all 103(a) rejections are "theoretical" because they are based on obviousness rather than anticipation. The rejection set forth previously provided technical reasoning to reasonably support the determination that anti-patched antibodies generated as taught by Tso et al against the mouse patched-2 protein taught by Motoyama would include antibodies that inherently bind to the human patched-2 protein of SEQ ID NO: 2. As set forth previously, the pool of antibodies generated against the mouse patched-2 polypeptide taught by Motoyama et al would inherently include antibodies that also bind to instant SEQ ID NO: 2 (human patched-2 polypeptide). The relevant art provides evidence that "the size of an epitope is approximately equivalent to 5-7 amino acids" (see pg 40 of Benjamini et al, 1991. Immunology: A Short Course, 2nd edition; cited previously; included here solely to support inherency). An alignment between the mouse patched-2 polypeptide taught by Motoyama et al and instant SEQ ID NO: 2 reveals numerous regions of 100% identity that comprise 5 or more amino acids (see the alignment of instant SEQ ID NO: 2 ("Qy") and the mouse patched-2 polypeptide taught by Motoyama et al ("Db") provided in the previous Office Action of 02 March 2009 at pages 4-5). For example, residues 82-119 share 100% identity, providing a stretch of 28 amino acids that are identical between the two proteins. Each region of exact identity of 5 or greater amino acids therefore contain identical epitopes that would inherently generate antibodies that would bind to either polypeptide. The term “specifically binds” is not defined in the specification as excluding antibodies that bind to the same epitope in other polypeptides (e.g., mouse patched-2); and therefore broadly encompasses antibodies that bind to the same epitope in two different sequences. Therefore, the set of antibodies generated against the mouse patched-2 polypeptide taught by Motoyama et al would inherently include antibodies that specifically bind to an epitope also found within the human polypeptide of SEQ ID NO: 2.

Applicants dispute that "any finding of the same 5-7 amino acids on two different proteins means that the two proteins contain the same "epitope"". Applicants cite Mayer (2009) in support as teaching that "the number of antigenic determinants per antigen is much lower than what would theoretically be possible".

These arguments have been fully considered but are not persuasive for the following reasons. The teachings of Mayer (2009) are not considered to provide evidence in support of Applicants' arguments. The Mayer reference is an outline of notes from a website that is subject to alteration at any time (and Applicants have not provided a dated copy of the reference) and that fails to provide any citations in the relevant literature for the quotations therein cited by Applicants. Thus, this is equivalent to submitting evidence in an unpublished manuscript. An unpublished manuscript is not proper evidence, since it has not been peer-reviewed and its contents have not been attested to under 37 CFR 1.132. Thus, Applicants' arguments with regard to this reference are considered attorney argument that is unsupported by evidence.

Applicants further argue that "Proteins are three-dimensional structures, so not all groupings of amino acids may be accessed by the antibodies such that binding occurs and such amino acid group is an "epitope." Further, "epitopes" may be linear stretches of amino acids … or may be a cluster of non-contiguous amino acids"

These arguments have been fully considered but are not persuasive for the following reasons. It is not disputed that proteins have three-dimensional structures. In Applicants' statement that "not all groupings of amino acid may be accessed by the antibodies such that binding occurs" it is not clear if Applicants are referring to antibodies produced from native or from linearized (unfolded by denaturation) proteins. If the native mouse Ptch2 protein were used to generate antibodies, all epitopes exposed while the protein has its native structure would be able to accessible to the antibodies produced. As shown in Figure 1b of Motoyama et al, the mouse Ptch2 protein has the same three-dimensional structure as the human PTCH protein (each is a twelve transmembrane domain protein), despite being less than 60% similar. Mouse Ptch2 has much greater similarity (89.3%; see pg 3 of the 3/2/09 Office Action) to the human Ptch2 of SEQ ID NO: 2, and the instant specification indicates that human Ptch2 is also a 12 transmembrane protein (¶ [0015]). Thus, the mouse Ptch2 and human Ptch2 protein have the same three-dimensional structure sharing 89.3% identity (1074 of 1182 amino acids). If the native mouse Ptch2 protein were used to generate antibodies, the same portions of the two highly homologous sequences would be

exposed to generate antibodies, and would generate antibodies that would bind to the same epitopes in either native protein. Furthermore, if unfolded mouse Ptch2 protein were used to generate antibodies, the entire amino acid sequence of the Ptch2 protein would be available to generate antibodies, and all epitopes exposed while the protein was unfolded would be accessible to the antibodies produced. Thus, it is maintained that all each region of exact identity of 5 or greater amino acids therefore contain identical epitopes that would inherently generate antibodies that would bind to either polypeptide.

Applicants further argue that "groupings of 5-7 amino acids in length may not be immunogenic, and therefore, would not constitute an "epitope" and the lack of immunogenicity may be explained by factors set forth in the abstract of Schellenkens et al (2005).

These arguments have been fully considered but are not persuasive for the following reasons. The teachings of Schellenkens concern the immunogenicity of therapeutic administered proteins (i.e., whether antibodies are generated by proteins when administered for therapy) and does not discuss the ability of a monoclonal antibody generated to an epitope in a particular protein to bind to the same epitope in a highly homologous protein.

Applicants further argue that "it is not true that a polyclonal serum may be generated in an animal against a given protein and will inevitably and always have cross-reactivity to the homologous protein of another species". Applicants cite Surman et al (1998) at pg 60 as teaching that "immunization of rabbits with nucleic acid encoding mouse tyrosinase (TRP-1) generated anti-mouse tyrosinase polyclonal serum that failed to react with human tyrosinase despite a 81% homology between human and mouse tyrosinase".

These arguments have been fully considered but are not persuasive for the following reasons. The teachings of Surman et al, which form the basis of the evidence supporting Applicants' argument, are directed to one specific type of experimental antibody generation that differs significantly from the general antibody teachings cited in the instant rejection. The teachings of Surman et al are limited to antibodies produced

by immunization with nucleic acids (DNA), rather than a protein, and Surman teaches that "vector characteristics" are variable that can result in differences in antibody production (pg 60). Furthermore, the instant claims, and the rejection thereof, are based on the production of monoclonal antibodies, not "polyclonal serum" as argued by Applicants and taught by Surman et al. Furthermore, the human and mouse Tyrosinase proteins taught by Surman et al have less (81%) homology than the human and mouse proteins of the instant rejection (89.3%). Furthermore, the polyclonal serum taught by Surman et al is limited to production in rabbits whereas the antibodies of the instant rejection are not so limited, but rather can be produced by any means encompassed by the teachings of Tso et al. Surman et al teaches difficulty in producing antibodies to the mouse protein in rabbits, indicating that the rabbit is not an optimal host for producing anti-mouse antibodies to Tyrosinase, perhaps because the similarity between the rabbit and mouse proteins results in low immunogenicity of the mouse protein in the rabbit (pg 60).

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647